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Effects of genetic polymorphisms of CYP1A1, CYP2E1, GSTM1, and GSTT1 on the urinary levels of 1-hydroxypyrene and 2-naphthol in aircraft maintenance workers

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Abstract

This study was undertaken to investigate the effects of genetic polymorphisms of the cytochrome P450 1A1 (CYP1A1) and 2E1 (CYP2E1), and glutathione S-transferases mu (GSTM1) and theta (GSTT1) on urinary 1-hydroxypyrene and 2-naphthol levels, and to estimate the level of exposure to polycyclic aromatic hydrocarbons (PAHs) in aircraft maintenance workers. In 218 Korean aircraft maintenance workers, the geometric means of urinary 1-hydroxypyrene and 2-naphthol were 0.32 and 3.25 μmol/mol creatinine, respectively. These urinary concentrations were approximately at the upper limit of the general population. Mean urinary 2-naphthol concentrations were significantly different between smokers and non-smokers. CYP1A1 and GSTM1 were statistically significant in analyses on both 1-hydroxypyrene and 2-naphthol levels among smokers. The results suggest that smoking has more profound effects on urinary PAH metabolites than does genetic polymorphisms in this population, and that CYP1A1 and GSTM1 activity might be related to the metabolism of 1-hydroxypyrene and 2-naphthol.

Keywords: 1-Hydroxypyrene; 2-Naphthol; Polycyclic aromatic hydrocarbons; Aircraft maintenance workers; Cytochrome P450; Glutathione S-transferase

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are natural components of most fossil fuels. They are formed by pyrolysis, incomplete combustion, or high-temperature processing of organic materials such as crude oil, coal, coke, or other industrial

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carbon compounds (Harrison, 1997; Schwarz-Miller et al., 1998). Epidemiological studies have shown an increased incidence of cancer among workers exposed to PAHs (Mastrangelo et al., 1996).

Aircraft maintenance workers are exposed to jet fuel and jet engine exhausts. Jet and diesel fuels are composed of hydrocarbons from the middle distillate fraction in the kerosene range, and the toxicity of both resembles that of kerosene (Cavender, 1996). Although jet fuel (kerosene) differs from motor fuel (petrol and diesel), exhaust emissions from the jet engines are essentially similar to those of internal combustion engines (Makker and Ayres, 1999; Tunnicliffe et al., 1999). Studies on workers exposed to diesel exhaust and on engine repair workers have shown higher levels of 1-hydroxypyrene (1-OHP) than in controls (Granella and Clonfero, 1993; Nielsen et al., 1996; Karahalil et al., 1998). These reports and a study reporting a higher urinary 1-OHP concentration in nautical engine room workers (Moen et al., 1996) lead to the supposition that aircraft maintenance workers are exposed to significant amounts of PAHs. However, data on PAH exposure in aircraft maintenance workers are scarce.

As the metabolism of PAHs is a complex process with high individual variation, markers related to exposure and metabolic capacity are useful in assessment of exposure and risk (Hemminki et al., 1997). Assessment of urinary 1-OHP levels may be a useful and cost effective indicator of exposure to PAHs (Jongeneelen, 1997), and urinary 2-naphthol (2-NAP) concentrations have been suggested to be a good route-specific biomarker for airborne PAHs (Jansen et al., 1995; Yang et al., 1999; Kim et al., 2001).

Inter-individual differences in the activity of enzymes involved in the metabolism and detoxification of PAHs may cause substantial variability in the biological response to the chemicals. Genetic polymorphisms of the enzymes have been suggested to explain inter-individual differences in the rate of metabolism and activation/deactivation of PAH-derived carcinogens (Alexandrie et al., 2000). There have been some recent reports on the relationship between genetic polymorphisms of bio-transformation enzymes, such as cytochrome P-450 (CYP), glutathione S-transferases (GSTs) and urinary concentrations of the PAH metabolites (Øvrebø et al., 1998; Merlo et al., 1998; Poirier et al., 1998; Yang et al., 1999).

Concentrations of urinary PAH metabolites are also influenced by behavioral factors, such as smoking and consumption of foods containing PAHs (Van Rooij et al., 1994; Merlo et al., 1998; Yang et al., 1999). When occupational exposure decreases, other sources of PAHs, such as food, tobacco smoking, environmental air pollution and drinking water, become relatively more important (Hemminki et al., 1997). In the present study, lifestyle factors, including smoking and consumption of grilled foods, were also considered.

The aim of this study was to investigate the effects of genetic polymorphisms of CYP1A1, CYP2E1, GSTM1 and GSTT1, and lifestyle factors on the levels of urinary 1-OHP and 2-NAP, and to estimate the levels of exposure to PAHs in aircraft maintenance workers.

2. Materials and methods

2.1. Study subjects and sample collection

The subjects were 218 male aircraft maintenance workers who worked at an air base in Korea. A self-completed questionnaire was used to obtain information about age, work duration, department of workplace, amounts and frequencies of cigarette smoking, duration of smoking, and amounts and frequencies of consumption of grilled meat and fish.

Peripheral blood was collected for analysis of the genetic polymorphisms of metabolic enzymes, and urine samples were taken for the analysis of metabolites of PAHs. The specimens were kept at -20 °C until analyzed.

2.2. Analysis of urinary 1-hydroxypyrene and 2-naphthol

Urinary 1-OHP and 2-NAP were determined using a high performance liquid chromatography system. Urinary 1-OHP was analyzed according to the method developed by Jongeneelen et al.

(1987), and 2-NAP was analyzed according to the method of Kim et al. (1999). 1-Hydroxypyrene and β-glucuronidase with sulfatase activity were purchased from Sigma (St. Louis, MO), and 2-NAP was from Aldrich (Germany). The HPLC system used was a Shimadzu (Kyoto, Japan) model LC-19AD, consisting of a pump (SPD-M10A), an automatic injector (SIL-10A), a fluorescence detector (RF-10AXL), and a CBM-10A Chromatopac integrator. The columns used were a 150 mm reverse-phase column (TSK-GEL ODS-80TM, TOSOH, Tokyo, Japan) for 1-OHP and a 250 mm reverse-phase column (Shim-pack CLC-ODS(M), Shimadzu) for 2-NAP. The mobile phases used were acetonitrile:water (56:44) for 1-OHP and acetonitrile:water (40:60) for 2-NAP, at a flow-rate of 1 ml/min. The retention times were 13.8 min for 1-OHP and 16.9 min for 2-NAP. The excitation/emission wavelengths for 1-OHP were 242/388 nm, and those for 2-NAP were 227/355 nm.

2.3. Determination of the genotypes

Genomic DNA was isolated from blood samples using a DNA purification kit (Promega, Madison, WI). The A4889G polymorphism in exon 7 of CYP1A1 that results in an Ile (CYP1A1*1A) to Val (CYP1A1*2C) amino acid replacement at residue 462 was determined by the PCR-restriction fragment length polymorphism method described by Oyama et al. (1995). Genotypes of CYP1A1 were classified into the *1A/*1A, *1A/*2C, and *2C/*2C. Genotypes of CYP2E1 were classified into the predominant homozygote alleles (*1A/*1A), the heterozygote alleles (*1A/*5B), and the rare homozygote alleles (*5B/*5B) (Kawamoto et al., 1995). A multiplex polymerase chain reaction (PCR) method was used to detect the presence or absence of the GSTM1 and GSTT1 genes in genomic DNA samples (Chen et al., 1996). PCR amplification for both GSTM1 and GSTT1 was carried out using β-globin as an amplification control indicator.

2.4. Statistical analysis

Data were statistically analyzed using SAS for Windows R 6.12. As urinary 1-OHP and 2-NAP concentrations were log-normally distributed, geometric means and geometric standard deviations were presented. Statistical methods included Student's *t* test and Pearson correlation analysis for the continuous variables and Spearman correlation analysis for the variables measured in ordinal scale. After stratification of smoking status, a multiple regression model was estimated for each stratum. In multiple regression models for non-smokers, the genotypes of CYP1A1, CYP2E1, GSTM1, and GSTT1 were included, and in the models for smokers, average smoking amounts and number of cigarettes on the day of sampling were added to those four genotypes.

3. Results

3.1. Characteristics of subjects

Results are expressed as means $\pm$ SDs. The mean age of the subjects was 32.17 ± 10.3 years, and the mean work duration was 11.29 ± 9.6 years. The numbers of workers in the base department and in the line maintenance department were 141 (64.4%) and 78 (35.6%), respectively. Characteristics of their smoking and consumption of grilled food are shown in Table 1.

3.2. Urinary concentration of PAH metabolites

There were no differences in the urinary 1-OHP and 2-NAP concentrations between workers in the base maintenance department and in the line maintenance department. Smoking was an important determinant of urinary concentrations of PAH metabolites. The urinary 2-NAP concentration of smokers was significantly higher than that of non-smokers (Table 2).

Table 2 shows the urinary concentrations of 1-OHP and 2-NAP from this study and some previous studies. The mean urinary 1-OHP concentration of this study was higher than the means of the general population but lower than those found in workers handling or producing coke oven, creosote, or graphite electrodes. In this study, the urinary 2-NAP concentration was higher in smokers than in Korean university students (Kim et al.,

2001), but lower than in both Korean shipyard workers (Kim et al., 2001) and Japanese office workers (Yang et al., 1999). However, the mean urinary 2-NAP concentration in the non-smoking subjects of this study was higher than in Korean shipyard workers (Kim et al., 2001), Korean university students (Kim et al., 2001), and Japanese office workers (Yang et al., 1999) who did not smoke.

3.3. Relations between genetic polymorphisms of metabolizing enzymes and urinary PAH metabolites

Table 3 shows correlation coefficients between

Table 1
Characteristics of smoking and consumption of grilled food

Categorical variables	Frequency (%)
Aircraft maintenance job	
Base maintenance (%)	141 (64.4)
Line maintenance (%)	78 (35.6)
Smoking status (number of persons)	
Non-smokers (%)	77 (35.5)
Smokers (%)	142 (64.5)
Smoking duration (years)	10.81 ± 7.97
Average daily number of cigarettes smoked	13.87 ± 6.26
Number of cigarettes smoked on the previous day	13.08 ± 6.85
Number of cigarettes smoked on the day of sampling	5.76 ± 4.51
Frequency of weekly consumption of grilled meat	
Seldom	17 (7.8)
1	126 (58.1)
2	53 (24.4)
3 or more	21 (9.7)
Frequency of weekly consumption of grilled fish	
Seldom	27 (12.3)
1	87 (39.7)
2	71 (32.4)
3 or more	34 (15.5)
Average consumption of grilled meat at one time (g)	
100	15 (6.8)
200	67 (30.6)
300	75 (34.2)
400 or more	62 (28.3)

Table 2
Geometric means (geometric standard deviations) of urinary concentrations of 1-hydroxypyrene and 2-naphthol of aircraft maintenance workers of this study and those of other population from other previous studies (μmol/mol creatinine)

	1-Hydroxypyrene	2-Naphthol
Aircraft maintenance workers	0.32 (1.84)	3.25 (1.92)
Smokers ($n = 141$)	0.32 (1.92)	3.74 (1.73)[a]
Non-smokers ($n = 77$)	0.30 (1.68)	2.53 (2.14)
Workers in other industries		
Korean shipyard workers (Kim et al. (2001))		
Smokers	0.44 (2.80)	4.44 (1.94)
Non-smokers	0.18 (2.40)	1.16 (3.06)
Coke oven workers (Jongeneelen et al. (1990))		
Smokers	3.37	–
Non-smokers	1.92	–
Coke oven workers (Malkin et al. (1996))	1.7	–
Creosote workers (Elovaara et al. (1995))	4–22	–
Graphite electrode workers (Ferreira et al. (1994))	1.68	–
Gate-keepers (Jongeneelen et al. (1988))		
Smokers	0.67	–
Non-smokers	0.47	–
Japanese office workers (Yang et al. (1999))		
Smokers	–	4.32 (2.51)
Non-smokers	–	0.71 (3.61)
Environmental exposure studies		
Korean university students (Kim et al. (2001))		
Smokers	0.04 (1.81)	3.62 (1.92)
Non-smokers	0.03 (1.71)	1.30 (2.13)
Canadian study (Viau et al. (1995))	0.08 (mean)	–
German study-3 area (Göen et al. (1995))	0.03, 0.09, 0.12	–

[a] $P < 0.01$ when compared with the mean urinary 2-naphthol concentration of non-smokers.

associated variables measured in continuous or ordinal scales and log-transformed concentrations of 1-OHP and 2-NAP. Among smokers, smoking duration, average smoking amount, smoking amount on the previous day, and smoking amount on the day of sampling were statistically significant. However, no variable showed significant correlation for non-smokers.

Table 4 shows the effects of genetic polymorphisms of CYP1A1, CYP2E1, GSTM1, and GSTT1 on urinary 1-OHP and 2-NAP. Among smokers, there were significant differences in mean urinary 1-OHP and 2-NAP concentrations associated with the CYP1A1 genotype.

Multiple regression analysis was performed to evaluate the effects of the genetic polymorphisms after controlling for the effects of personal and behavioral factors. Either the amount smoked on the previous day or the amount smoked on the sampling day was included into the model, because these two variables demonstrated multicollinearity. There was no significant multiple regression among non-smokers (Table 5). In the multiple regression analyses in smoking aircraft maintenance workers, CYP1A1 and GSTM1 were significant for urinary 1-OHP level, and CYP1A1, GSTM1, average daily smoking amounts, and smoking amounts on the sampling day for urinary 2-NAP concentration (Table 5).

Table 3
Correlation coefficients between personal or behavioral variables and log-transformed concentration of urinary PAH metabolites among smokers

Variables	1-Hydroxypyrene	2-Naphthol
Age	0.13	0.09
Work duration	0.12	0.03
Frequency of weekly consumption of grilled meat[a]	0.04	0.12
Frequency of weekly consumption of grilled fish[a]	0.04	0.07
Average consumption of grilled meat at one time[a]	−0.06	−0.05
Smoking duration	0.19[b]	0.14
Average daily number of cigarettes smoked	0.12	0.36[c]
Number of cigarettes smoked on the previous day	0.15	0.35[c]
Number of cigarettes smoked on the day of sampling	0.11	0.35[c]

[a] Spearman correlation coefficients.
[b] $P<0.05$.
[c] $P<0.01$.

4. Discussion

The sample size of this present study, 218, is larger than the appropriate sample size (164) required for the study of individual assessment of environment exposure to PAHs (Siwińska et al., 1998). Urinary 1-OHP concentrations in the aircraft maintenance workers were lower than those in coke oven workers, in Finnish creosote workers (Elovaara et al., 1995), or in Belgian graphite electrode workers (Ferreira et al., 1994). However, they were higher than those found in Korean middle school students (Kang et al., 2000), or in the Canadian (Viau et al., 1995) or the German general population (Göen et al., 1995) not occupationally exposed to PAHs. These results suggest that the level of PAH exposure of aircraft maintenance workers may be close to or slightly above the upper limit of the general population, based on urinary 1-OHP levels.

Cigarette smoking has been a significant determinant of urinary 1-OHP concentrations in many previous studies (Granella and Clonfero, 1993; Göen et al., 1995; Gilbert and Viau, 1997; Hara et al., 1997; Merlo et al., 1998; Yang et al., 1999; Alexandrie et al., 2000). In the present study, however, a significant association was not found between smoking and urinary 1-OHP concentrations. One possible explanation for this inconsistency is the high level of urinary 1-OHP in the non-smokers of this study. The mean urinary 1-OHP concentration in non-smoking aircraft maintenance workers, 0.30 μmol/mol creatinine,

Table 4
Geometric means (geometric standard deviations) of urinary 1-hydroxypyrene and 2-naphthol concentrations according to genetic polymorphisms of CYP1A1, CYP2E1, GSTM1, and GSTT1 (μmol/mol creatinine)

	N	Smokers		Non-smokers	
		1-Hydroxypyrene	2-Naphthol	1-Hydroxypyrene	2-Naphthol
CYP1A1					
*1A/*1A	111	0.28 (1.92)	3.46 (1.80)	0.28 (1.55)	2.56 (2.36)
*1A/*2C	97	0.40 (1.79)[a]	4.35 (1.58)[a]	0.34 (1.80)	2.59 (1.95)
*2C/*2C	12	0.23 (2.01)	2.41 (1.54)	0.24 (1.48)	2.64 (2.29)
CYP2E1					
*1A/*1A	137	0.34 (1.95)	3.86 (1.80)	0.29 (1.57)	2.59 (1.97)
*1A/*5B	73	0.30 (1.86)	3.32 (1.58)	0.33 (1.93)	2.72 (2.51)
*5B/*5B	8	0.53 (1.28)	4.26 (1.62)	0.38 (1.86)	1.75 (1.95)
GSTM1					
Present	87	0.36 (1.99)	4.14 (1.68)	0.30 (1.77)	2.86 (2.48)
Null	131	0.30 (1.84)	3.49 (1.75)	0.31 (1.67)	2.41 (1.88)
GSTT1					
Present	115	0.36 (1.92)	4.06 (1.73)	0.30 (1.70)	2.34 (1.82)
Null	103	0.29 (1.88)	3.42 (1.72)	0.30 (1.72)	2.89 (2.48)

[a] $P<0.01$ when compared with CYP1A1*1A/*1A group.

was higher than the mean value in non-smoking Korean shipyard workers, 0.18 μmol/mol creatinine, and the 95th percentile value in the non-smoking individuals who were not occupationally-exposed to PAHs, 0.24 μmol/mol creatinine (Jongeneelen, 2001). This result supports the possibility that aircraft maintenance workers are exposed to considerable amounts of PAHs from sources other than cigarette smoking. The number of cigarettes smoked in study could be another explanation for the absence of difference in urinary 1-OHP concentrations between smokers and non-smokers. The average daily number of cigarettes smoked in this study, 13.87, was about two-thirds of the corresponding value for Japanese office workers, 22.1 (Yang et al., 1999).

A significant association between cigarette smoking and urinary 2-NAP concentrations was found as in a study on Japanese office workers (Yang et al., 1999) and in another on Korean shipyard workers (Kim et al., 2001). These could be explained by the fact that cigarette contains 100 times more naphthalene than pyrene (Schmelz et al., 1976; Grimmer et al., 1987). Nevertheless, cigarette smoking does not seem to be the unique source of naphthalene. Concentrations of total suspended particles in urban air showed a good correlation with urinary 2-NAP concentrations in non-smoking male Korean middle school students (Kang et al., 2000).

CYP1A1 was a significant factor in both univariate and multivariate analyses for the two PAH metabolites in this study. As observed in previous studies (Alexandrie et al., 2000; Nerurkar et al., 2000), the highest 1-OHP and 2-NAP level was observed in smokers with the CYP1A1*1A/*2C genotype (Tables 4 and 5). However, we could find no significant difference in the urinary concentrations of 1-OHP and 2-NAP associated with the CYP1A1 genotype among non-smoking aircraft maintenance workers. In a study of Chinese coke plant workers, the CYP1A1 Ile/Val polymorphism, but not the CYP1A1 *Msp*I polymorphism, was observed to affect PAH-DNA adduct levels (Pan et al., 1998). In a previous study of Italian coke oven workers, significant correlations were recognized between the DNA adduct and urinary 1-OHP levels among subjects with the CYP1A1 Ile/Val and

Val/Val genotypes, but not among the coke oven workers with the Ile/Ile genotype (Brescia et al., 1999). The data obtained in these studies and our present study are consistent with the suggestion that individuals with the CYP1A1*2 allele have a greater capacity to activate PAHs from tobacco smoke and occupational exposure and, as a result, are at greater risk for PAH-related cancers, especially certain respiratory cancers (Nerurkar et al., 2000).

CYP2E1 was a significant determinant of urinary concentrations of 2-NAP in Japanese office workers, especially in smokers (Yang et al., 1999). The expression of CYP2E1 mRNA in the CYP2E1*1A/*5B or CYP2E1*5B/*5B type was higher than in the CYP2E1*1A/*1A type in human peripheral lymphocytes (Watanabe et al., 1994), and the induction of CYP2E1 is known to increase the formation of naphthols from naphthalene (Wilson et al., 1996). In this present study, however, neither urinary concentrations of 1-OHP nor those of 2-NAP showed significant differences between the *1A/*1A and the *1A/*5B or *5B/*5B genotypes of CYP2E1. This would be partly because the average daily smoking amounts, and therefore the levels of urinary 2-NAP, were relatively lower in the aircraft maintenance workers who smoked in this study than in the Japanese office workers previously studied (Yang et al., 1999). Because ethanol induces CYP2E1 (Pavanello and Clonfero, 2000), the absence of difference in urinary 1-OHP and 2-NAP level might be partly due to the confounding effect of ethanol intake. We did not control for alcohol consumption in the comparison of urinary 1-OHP and 2-NAP concentrations associated to the CYP2E1 genotype of aircraft maintenance workers.

GSTM1 was not significant in the univariate analyses for 1-OHP and 2-NAP. However, the presence of GSTM1, together with the amounts of daily cigarette smoking and amount of cigarette smoking on sampling day, was significant in the multiple regression against 2-NAP among smokers. GSTM1 was a significant determinant of urinary 2-NAP level in a previous study with Japanese office workers (Yang et al., 1999), in which the statistical significance of GSTM1 disappeared when 2-NAP concentrations corrected for

Table 5
Multiple regression analysis of log-transformed concentration of 1-hydroxypyrene and 2-naphthol in aircraft maintenance workers

Independent variables	Ln(1-Hydroxypyrene)			Ln(2-Naphthol)		
	β[a]	SE[b] (β)	P value	β[a]	SE[b] (β)	P value
Non-smokers		$R^2 = 0.01$			$R^2 = 0.04$	
CYP1A1	−0.10	0.07	0.15	<0.01	0.09	0.99
CYP2E1[c]	0.16	0.13	0.24	−0.05	0.18	0.80
GSTM1	−0.04	0.14	0.74	0.22	0.19	0.23
GSTT1	−0.01	0.13	0.94	−0.25	0.18	0.17
Smokers		$R^2 = 0.13$			$R^2 = 0.26$	
Smoking 1[d]	0.01	0.01	0.40	0.02	0.01	<0.01
Smoking 2[e]	0.01	0.01	0.54	0.02	0.01	0.03
CYP1A1	−0.17	0.06	<0.01	−0.10	0.04	0.01
CYP2E1[c]	−0.10	0.11	0.37	−0.07	0.08	0.39
GSTM1	0.22	0.11	0.04	0.21	0.08	0.01
GSTT1	0.09	0.11	0.39	0.07	0.08	0.40

[a] Regression coefficient.
[b] Standard error.
[c] Subjects were divided into two groups according to their CYP2E1 isozyme status: CYP2E1*1A/*1A vs. CYP2E1*1A/*5B or CYP2E1*5B/*5B.
[d] Average number of cigarettes smoked.
[e] Number of cigarettes smoked on the day of sampling.

creatinine were included in the model as the dependent variable instead of the uncorrected value. Based on the result that the effects of GSTM1 polymorphisms on urinary 1-OHP levels was significant only in the multiple regression analysis but not in the simple comparison, Alexandrie et al. (2000) suggested that GSTM1 activity may be indirectly linked to the metabolism of 1-OHP. The results of Merlo et al. (1998) and Øvrebø et al. (1998) also seem to imply an indirect relation between genetic polymorphisms of metabolizing enzymes with PAH-exposure biomarkers.

Heterozygosity for GSTM1 could explain this indirect action of GSTM1. A weakness of epidemiological studies on GSTM1 is that individuals heterozygous for GSTM1 cannot be identified, and have therefore been included in the GSTM1-present group (Autrup, 2000). We did not identify heterozygotes for GSTM1 in this present study, either. If we were to classify GSTM1 genotype into three types (homozygously deleted, heterozygous, and homozygously present), there could be the possibility of a significant linear trend of urinary 1-OHP or 2-NAP concentration, according to the GSTM1 genotype in univariate analysis. Another possible explanation is that glutathione-conjugated 2-NAP was not detected at the excitation/emission wavelengths used to detect unconjugated 2-NAP. A deficiency in GSTM1 may stimulate the glucuronidation pathway by the accumulation of PAH derivatives that are otherwise conjugated to glutathione (Vaury et al., 1995). If this were the case, the differences in urinary concentrations of glucuronide-conjugated PAHs between GSTM1-present and GSTM1-null individuals would increase in individuals who are exposed to higher concentrations of PAHs.

Neither urinary 1-OHP nor 2-NAP concentrations were higher in GSTT1-positive aircraft maintenance workers than in GSTT1-null workers. In our data on Korean coke oven workers, urinary 1-OHP concentrations in GSTT1-positive workers were not significantly higher than in GSTT1-null subjects (Nan et al., 2001). Urinary 1-OHP levels were not significantly influenced by polymorphic variations in GSTT1 in the other ethnic groups studied (Poirier et al., 1998; Brescia et al., 1999). Although there has been a study that reported a higher 1-OHP-glucuronide excretion in GSTT1-positive smokers than in GSTT1-null smokers (Hong et al., 1999), it is unlikely that GSTT1 polymorphism plays an important role in the metabolism of naphthalene or pyrene.

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